Clodoveo Ferri

Studies on the Potential Role of Infectious and Toxic Factors in the Etiopathogenesis of Systemic Sclerosis

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Insights into the knowledge of complex diseases: Environmental infectious/ toxic agents as potential etiopathogenetic factors of systemic sclerosis

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2023

Viruses:

- Parvovirus B19
- Human Cytomegalovirus
- Human herpesvirus 6A
- Retroviruses
- SARS-CoV-2

Chemicals/Toxics:

- Silica

Table 1
Systemic sclerosis (SSc): main putative etiological factors, pathogenetic mechanisms and outcomes. VIRUSES.

	Immune system	Ref. No.	Endothelial cells	Ref. No.	Fibroblasts	Ref. No.
	Mechanisms/*Effects*		Mechanisms/*Effects*		Mechanisms/*Effects*	
Human Cytomegalovirus (HCMV)	**Significantly higher levels of antibodies against HCMV-derived UL94 protein in serum of SSc patients**/*Molecular mimicry between UL94 and self-peptides expressed on endothelial cells and dermal fibroblasts*	[44,50, 52]	**Antibodies directed against UL94**/*Recognition of membrane receptors of endothelial cells (NAG-2) with subsequent apoptosis of endothelial cells and expression of genes functionally associated with clinical signs of SSc (molecular mimicry mechanism)*	[44]	**Antibodies directed against UL94**/*Recognition of membrane receptors of dermal fibroblasts (NAG-2) with activation of fibroblasts and subsequent expression of genes functionally associated with clinical signs of SSc (molecular mimicry mechanism)*	[50]
	Significantly higher levels of antibodies against HCMV-derived protein pp65 in serum of SSc patients/*Higher frequency of SSc-associated autoantibodies*	[36,51]	**Detection of viral transcripts in endothelial cells from skin biopsy of a woman with SSc diagnosed after an acute HCMV infection**/*Possible triggering role for HCMV*	[49]	**Increased expression of pro-fibrotic factors**/*Fibrosis induction in fibroblasts*	[72]
	Increase of HCMV-specific $CD8^+$ T cell responses in SSc patients vs healthy subjects/*Statistically significant association with some of the most relevant disease parameters*	[65]			**Increased expression of fibrosis-associated microRNAs**/*Fibrosis induction in fibroblasts*	[73]
Human Herpesvirus-6A (HHV-6A)	**Increased prevalence/titer of anti-HHV-6 U94 antibodies**/*Multiple HHV-6 reactivations?*	[109]	**Increased expression of pro-fibrotic factors**/*Fibrosis induction in endothelial cells*	[109]	***Increased expression of pro-fibrotic factors***/*Fibrosis induction in fibroblasts*	[72]
	Impaired anti-HHV-6 NK response/*Uncontrolled HHV-6 infection and reactivation*	[109]	**Induction of HLA-G**/*Inhibition of angiogenesis*	[106]	**Increased expression of fibrosis-associated microRNAs**/*Fibrosis induction in fibroblasts*	[73]
Parvovirus-B19 (B19V)	**NLRP3 inflammasome activation**/*Immune-mediated inflammatory tissue damages evolving in fibrosis*	[152]	**CACs apoptosis and impaired mobilization**/*Neo-vascularization defects, diffuse microangiopathy, ischemic tissue damages*	[124, 148]	**Fibroblasts activation, increased migration, invasiveness and expression of profibrotic factors**/*Fibrosis induction in fibroblasts*	[146]
Retroviruses	**Antibodies to retroviral proteins in sera from SSc patients. Sequence homologies between specific retroviral proteins and the topoisomerase I antigen (target of anti-Scl 70 antibodies)**/*Molecular mimicry*	[16]	**Experimentally induced expression of retroviral proteins in normal human dermal fibroblasts**/*Acquisition of a SSc-like phenotype and production of extracellular matrix proteins*	[16]		

Abbreviations: UL94 (Unique Long HCMV genomic sequence encoded 94 KDa tegument protein); NAG-2 (Novel antigen-2); pp65 (65 KDa tegument phosphoprotein); U94 (HHV-6 unique gene 94 product); NK (Natural-killer cells); HLA-G (Human Leukocyte Antigen-G); NLRP3 (Nod-Like Receptor pyrin domain containing 3); CACs (Circulating angiogenic cells).

1999

RAPID PAPER

Clinical and Experimental Rheumatology 1999; 17: 718-720.

Parvovirus B19 infection of bone marrow in systemic sclerosis patients

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Key words:
Systemic sclerosis, scleroderma, parvovirus B19, bone marrow.

ABSTRACT

Objective

To investigate the prevalence of human parvovirus B19 (B19) infection in the bone marrow of systemic sclerosis (SSc) patients.

Methods

Twenty-one consecutive SSc patients and 15 sex- and age-matched subjects without immunological rheumatic diseases were studied for: (i) the presence of circulating anti-B19 antibodies (anti-B19 IgG and IgM type and anti-B19 NS1 IgG) detected by means of standard methodologies, and (ii) B19 genomic sequences in sera and bone marrow biopsy specimens using a nested-PCR technique.

Results

The presence of B19 DNA was demonstrated in a significant percentage of bone marrow biopsies from SSc patients (12/21; 57%) and was never detected in the control group ($p < 0.01$). In no case was the B19 viremia observed, while serum anti-B19 NS1 antibodies, possible markers of B19 persistent infection, were more frequently detected in SSc patients than in controls (33% vs 13%). SSc patients with bone marrow B19 infection showed a shorter mean disease duration than B19-negative patients (5.6 ± 4.2 vs 12.7 ± 7.8 yrs; $p < 0.01$).

Conclusions

This is the first demonstration of bone marrow B19 infection in a significant percentage of SSc patients. The possible etiopathogenetic role of B19 should be verified in a larger patients series and further investigated by means of molecular biology studies.

proposed as a causative agent for some rheumatic disorders, such as rheumatoid arthritis and the systemic vasculitides (3), we began to study the prevalence of serum B19-related markers in SSc patients (4). Viremia was detected in 4% of SSc patients, a very high rate in comparison with that of healthy blood donors, which does not exceed 0.6% (5). Moreover, the presence of anti-B19 IgG, but not anti-B19 IgM, in the serum of B19 DNA-positive SSc patients suggested a persistent infection (4).

This preliminary observation prompted us to further investigate the possible pathogenetic involvement of this virus in SSc. Given the B19 tropism for various organs, due to the broad distribution of its cellular receptor (6), particularly in bone marrow tissue, we investigated the prevalence of B19 infection in bone marrow biopsies from patients with SSc compared with a control group of subjects without immunological rheumatic disorders.

Patients and methods

Twenty-one unselected SSc patients (5 M, 16 F, mean age ± SD: 49 ± 12 yrs., mean disease duration: 9 ± 7 yrs.) and a control group of 15 sex- and age-matched subjects without immune-mediated rheumatic disorders (6 healthy bone marrow donors, and 1 monoclonal gammopathy, 4 non-Hodgkin's lymphoma, and 4 multiple myeloma patients) were included in the study. All of the SSc patients met the American College of Rheumatology (formerly, American Rheumatism Association) 1980 preliminary criteria for the classification of the disease (7). Patients were consecutively recruit-

Persistent PV-B19 infection
of bone marrow in a significant percentage of SSc patients may present important pathological implications, among which we can hypothesize that the virus might

- exert a chronic stimulus for the immune system leading to the immunological abnormalities observed in SSc,
  and/or
- it might be responsible for the impaired production of endothelial progenitors by bone marrow mesenchymal stem cells.

First observation of systemic sclerosis following recent cytomegalovirus infection in a young lady with genetic predisposition to autoimmunity (mother affected by systemic lupus erythematosus)

2002

Systemic sclerosis following human cytomegalovirus infection

C Ferri, M Cazzato, D Giuggioli, M Sebastiani, C Magro

Ann Rheum Dis 2002;**61**:0–1

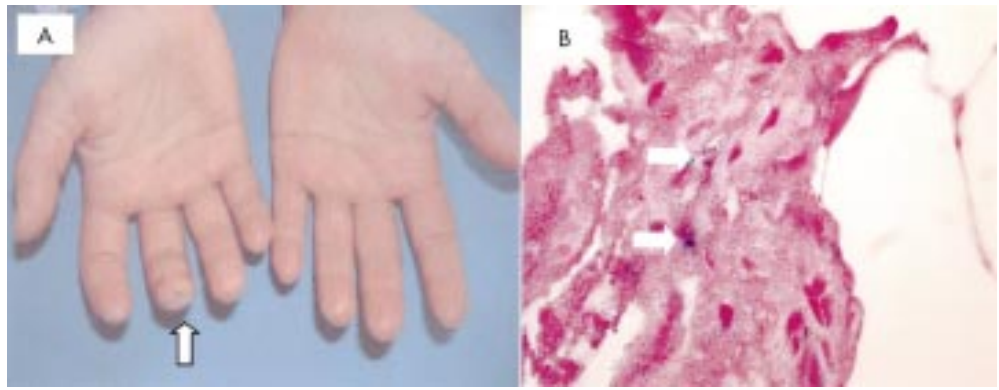

Figure 1 (A) Sclerodactyly and skin ulcer in the third fingertip of the right hand (arrow); (B) skin biopsy: reverse transcriptase-polymerase chain reaction in situ for HCMV RNA showing granular nuclear staining of endothelial cells (arrows).

Nature Medicine **volume 6**, pages 1183–1186 (2000)

Systemic sclerosis immunoglobulin G autoantibodies bind the human cytomegalovirus late protein UL94 and induce apoptosis in human endothelial cells

Claudio Lunardi, Caterina Bason, Riccardo Navone, Enrico Millo, Gianluca Damonte, Roberto Corrocher & Antonio Puccetti

2020

microorganisms

MDPI

Article

HHV-6A Infection and Systemic Sclerosis: Clues of a Possible Association

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Abstract: Systemic sclerosis (SSc) is an autoimmune disease characterized by vasculopathy, excessive extracellular matrix deposition, and fibrosis of the skin and internal organs. Several infectious agents, including human herpesvirus-6 (HHV-6), have been suggested as possible triggering factors, but a direct association is still missing. We characterized 26 SSc patients for the presence of HHV-6 in tissues and blood, the anti-HHV-6 response, HLA-G plasma levels, and KIR typing. Given the prominent role of endothelial cells (EC) in SSc pathogenesis, along with HHV-6 tropism for EC, we also investigated the expression of pro-fibrosis factors in HHV-6 infected EC. Results showed the presence of HHV-6A in skin biopsies, and an increased virus load was associated with disease severity and poor natural killer (NK) response against the virus, particularly in subjects exhibiting a KIR2 phenotype. HLA-G plasma levels were significantly higher in HHV-6A/B-KIR2 positive SSc patients and in vitro HHV-6A infection-induced pro-fibrosis factors expression in EC, supporting its role in the development of the fibrosing process. Our data suggest an association between virus infection/reactivation and disease, opening the way to future studies to understand the mechanisms by which HHV-6A might contribute to the multifactorial pathogenesis of SSc.

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journal homepage: www.elsevier.com/locate/semarthrit

High serum levels of silica nanoparticles in systemic sclerosis patients with occupational exposure: Possible pathogenetic role in disease phenotypes

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ARTICLE INFO

Keywords:
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Scleroderma
Silica
Occupational exposure
Etiopathogenesis
Microparticles
Nanoparticles
Interstitial lung fibrosis

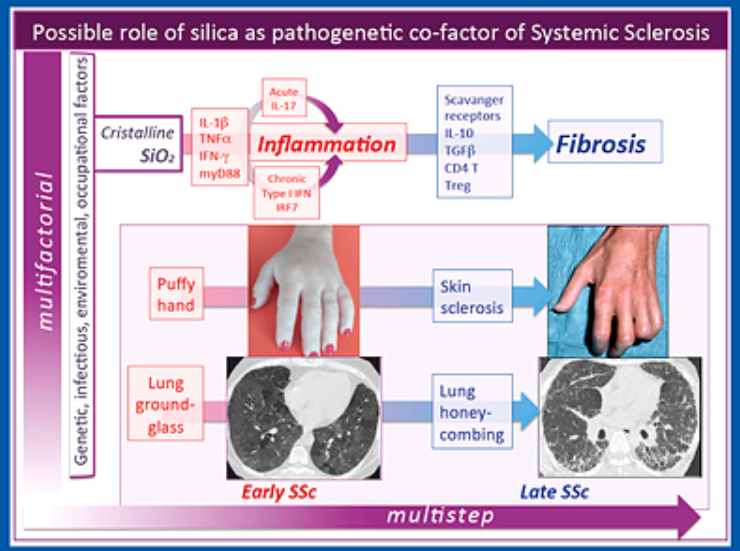
ABSTRACT

Background: Systemic sclerosis (SSc) is an autoimmune systemic disease characterized by diffuse fibrosis of skin and visceral organs due to different genetic, infectious, and/or environmental/occupational causative factors, including the inhalation of silica dust.
Objectives: To investigate serum trace elements including silicon (s-Si) levels in SSc patients living in a restricted geographical area with high density of worksites with silica exposure hazard.
Methods: This case-control study included 80 SSc patients (M:F 10:70; aged 58.4 ± 11.9SD years, mean disease duration 10.1 ± 7.8SD) and 50 age-/sex-matched healthy control subjects consecutively investigated at our University-based Rheumatology Unit. Patients and controls were evaluated for environmental/occupational exposure categories (structured questionnaire), morphological characterization of serum micro-/nanoparticles (Environmental Scanning Electron Microscopy and Energy Dispersive X-ray Spectroscopy microanalysis), and quantitative assessment of trace elements (inductively coupled plasma atomic emission spectroscopy).
Results: Among various categories, only occupational exposure to silica dust was recorded in a significant proportion of SSc patients compared to controls (55% vs. 11%; $p < .0001$). Qualitative analysis showed serum silica micro- and nanoparticles in all exposed patients. Quantitative evaluation evidenced significantly higher s-Si levels in SSc patients versus controls ($p < .0001$); in addition, higher s-Si levels were detected in patients with occupational exposure ($p < .0001$), diffuse cutaneous SSc ($p = .0047$), myositis ($p = .0304$), and/or lung fibrosis ($p = .0004$) compared to those without; notably, the severity of lung fibrosis scoring positively correlated with s-Si levels ($p < .0001$).
Conclusions: The study first demonstrated high s-Si levels in exposed SSc patients; this element might represent a pathogenetic co-factor of more severe clinical phenotypes, mainly diffuse scleroderma with lung fibrosis.

2018

Volume 48 , Number 3 December 2018

SEMINARS IN ARTHRITIS & RHEUMATISM



Possible role of occupational/environmental exposure to silica dust as pathogenic co-factor in systemic sclerosis

EDITOR:
Marc C. Hochberg, MD, MPH

W.B. SAUNDERS

Table 2
Systemic sclerosis (SSc): main putative etiological factors, pathogenetic mechanisms and outcomes. CHEMICALS.

	Immune system	Ref. No.	Endothelial cells	Ref. No.	Fibroblasts	Ref. No.
	Mechanisms/*Effects*		Mechanisms/*Effects*		Mechanisms/*Effects*	
Silica (Si)	**IL-2 receptor decrease, increase of IFN-gamma, IL-1β, TNF-alfa, IL-6, IL-10 and TGF-β cytokines**/*Immune activation and lymphoproliferation*	[175]	**IL-8 release**/*Cytotoxic effect in mono- and in coculture with A549 alveolar epithelial cells and microvascular cells*	[177]	**Si induced macrophages miRNAs led to myofibroblast transition**/*Critical role in lung damage and fibrosis*	[181]
	NALP3 inflammasome-driven IL-1β increase, Scavenger receptors activation, macrophages apoptosis/*Inflammasome activation, lung inflammation and fibrosis, silicosis*	[178]	**Si O2-induced increased cell proliferation, migration, and changes in endothelial cells; increased expression of mesenchymal markers**/*Lung fibrosis*	[179]	**Silica gel induced collagen and MAP kinase phosphorylation on human dermal fibroblasts**/*Silica gel directly cause fibrotic phenotype*	[182]
	Si NPs trigger cytokine inflammatory response and induce oxidative stress/*Inflammation of human peripheral blood mononuclear cells*	[176]	**Si NPs induced significant calcium mobilization and ROS generation**/*Decreased the viability and damaged the plasma membrane of cultured HUVECs*	[180]	**Si NPs lead to cell necrosis in a dose-dependent manner**/*Fibroblast cell necrosis*	[183]

Abbreviations: IL (interleukin); TGF (transforming growth factor); IFN (interferon); TNF (tumor necrosis factor); NALP (nucleotide-binding oligomerization domain, leucine rich repeat and pyrin domain containing); NPs (nanoparticles); ROS (reactive oxygen species); HUVEC (human umbilical vein endothelial cells); miRNA (microRNA); MAP kinase (mitogen-activated protein kinase).

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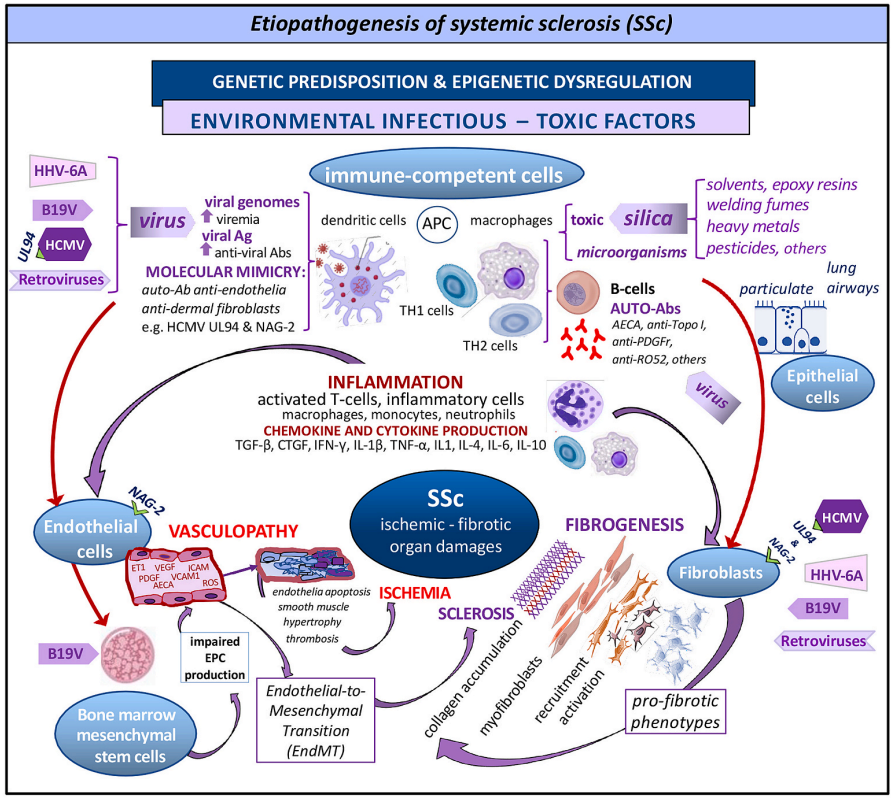
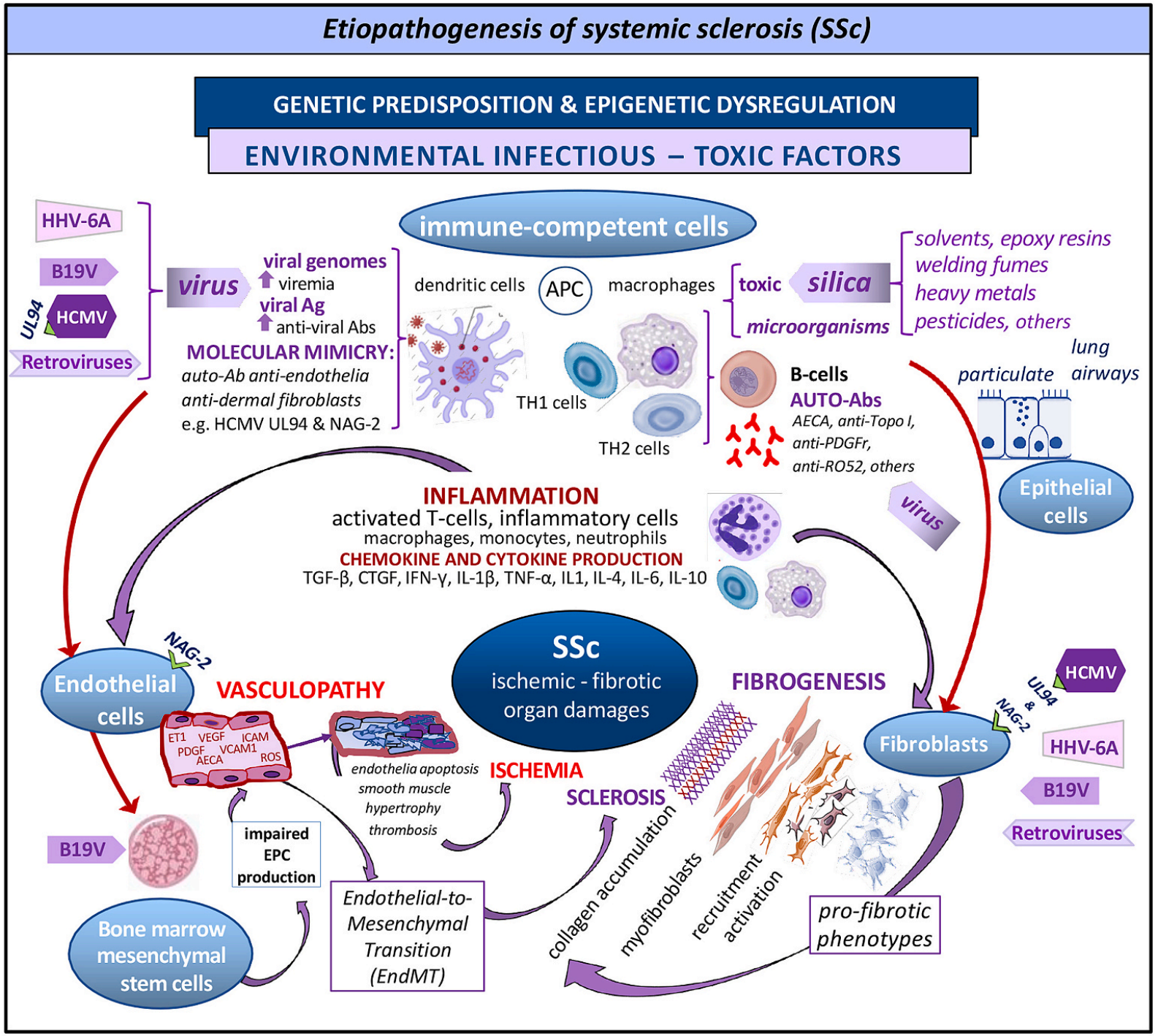


Fig. 1. Putative etiopathogenetic network of systemic sclerosis. The etiopathogenesis of systemic sclerosis (SSc) encompasses a genetically-driven predisposition with the possible contribution of epigenetic modifications, immune-system dysregulation, diffuse microangiopathy, and abnormal collagen tissue deposition by altered fibroblasts. These mechanisms are probably triggered/sustained by variable combination of environmental factors (*i.e.*: infectious/physical/chemicals) through a multistep process. Briefly: **(i) host genetic predisposing factors and epigenetic dysregulation** have a prominent role in the SSc pathogenesis, commonly recognized but not plainly documented; **(ii) remote events** may precede even by years the clinical SSc onset; *i.e.* the exposure to **toxic agents** such as vinyl chloride or silica dust and/or **latent viral infections**, which may affect different target tissues: dendritic cells, macrophages, fibroblasts, endothelial, airway epithelial, immune-competent cells, and extracellular matrix. With respect to viral infections, they may trigger both innate and adaptive immune system with T- and B-lymphocyte activation, antigen-dependent oligoclonal lymphocyte expansion, and specific autoantibody production. The antigen-driven response (**molecular mimicry mechanism**) has been suggested on the basis of sequence homologies between specific viral proteins and self-Ag (*i.e.*: HCMV protein UL94 and self-peptides NAG-2 expressed on endothelial cells and dermal fibroblasts, specific retroviral proteins and topo-I antigen). Molecular mimicry can be responsible for both $CD8^+$ T-lymphocyte and/or autoantibody-mediated endothelial/fibroblast injury, myofibroblast transition, with ischemic and fibrotic organ damage; **(iii) endothelial dysfunction and apoptosis are crucial for both scleroderma vasculopathy and fibrogenesis.** Endothelia are the primarily SSc target cells (reversible digital ischemia of Raynaud's phenomenon is the presenting symptom of SSc in the majority of cases); a direct (viral infection, oxidative stress, toxic agents) or immune-mediated (AECA) endothelial cell damage may lead to severe vascular alterations (sub-endothelial fibrosis, muscular proliferation, and vessel deletion/thrombosis) and ultimately to ischemic lesions. B19V chronic infection of bone marrow might be responsible of impaired production of circulating EPCs with marked consequence for scleroderma microangiopathy. Endothelial to mesenchymal transdifferentiation may contribute to scleroderma fibrogenesis; several proinflammatory and profibrotic cytokines (TGF-β, CTGF, IL-1, TNF-α), chemokines, hypoxia, and autoantibodies (AECA) can be involved in this process; **(iiii) fibroblast transformation into pro-fibrotic phenotypes with collagen hyper-production and tissue accumulation** may be the consequence of direct and/or immune-mediated (molecular mimicry) cell injury; the latter may be promoted by both viral infections and/or toxic agents such as cristallina silica. The myofibroblasts recruited from different sources (resident fibroblasts, bone marrow stem cells, and/or endothelial/epithelial to mesenchymal transdifferentiation) may concentrate at the extracellular matrix and produce excessive collagen accumulation with fibrotic organ damage.

Abbreviations: HHV-6A: human herpes virus-6A; B19V: parvovirus B19; HCMV: human cytomegalovirus; UL94 (Unique Long HCMV genomic sequence encoded 94 KDa tegument protein); Ag: antigen; Abs: antibodies; vertical violet arrows (↑): increased levels; APC: antigen presenting cells; TH: T helper lymphocytes; AECA: anti-endothelial cell antibodies; anti-Topo I: anti-topoisomerase I (Scl70) Abs; anti-PDGFr: anti-platelet derived growth factor receptor Abs; TGF-β:transforming growth factor beta; CTGF: connective tissue growth factor; IFN-γ: interferon gamma; IL: interleukin; TNF-α: tumor necrosis factor-α; NAG-2 (Novel antigen-2); ET1: endothelin 1; VEGF: vascular endothelial growth factor; ICAM: intercellular adhesion; PDGF: platelet derived growth factor; VCAM-1: type 1 vascular cell adhesion molecules; ROS: reactive oxygen species.

2021



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Multifactorial and multistep etiopathogenesis of systemic sclerosis

2021

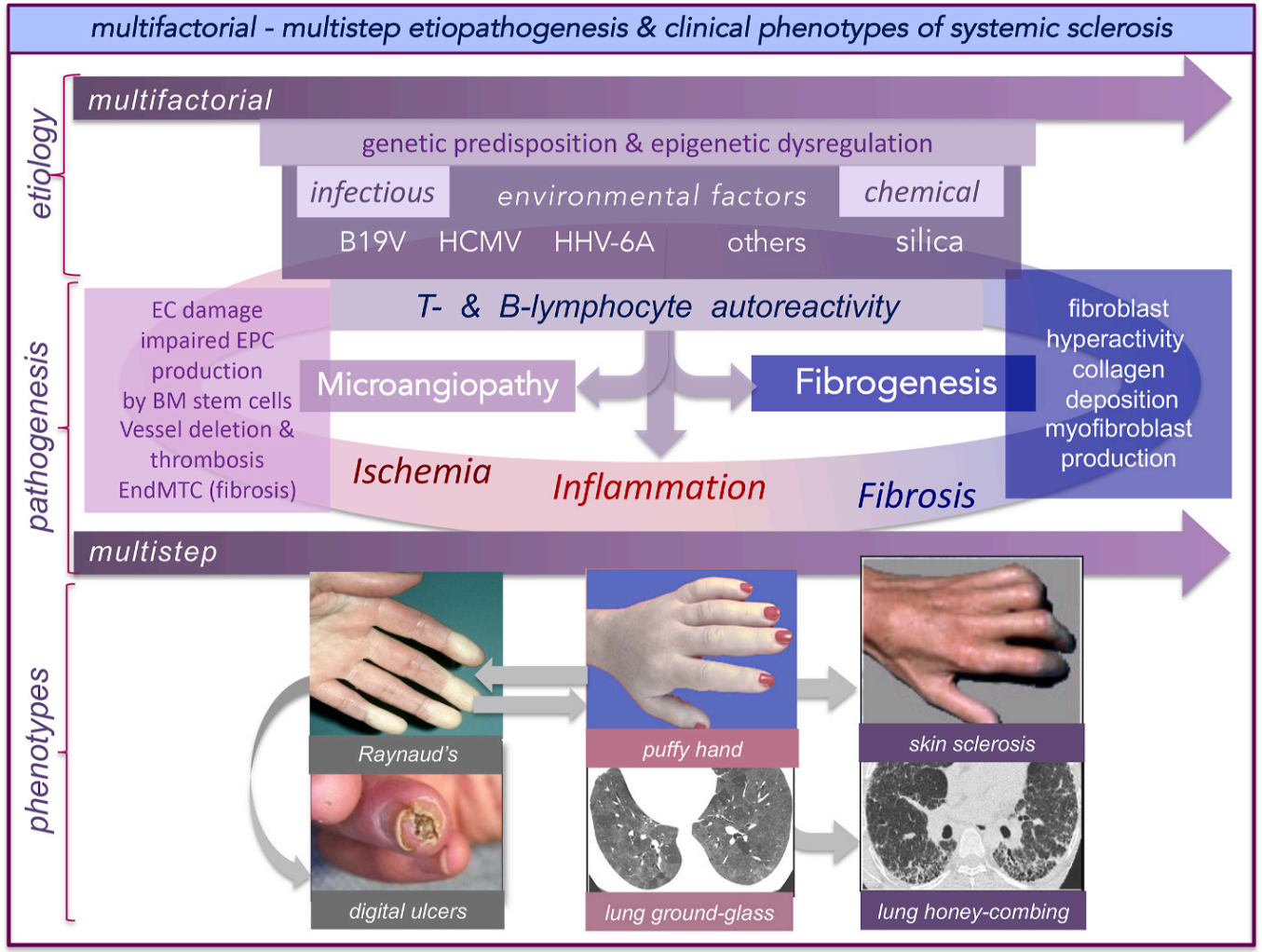
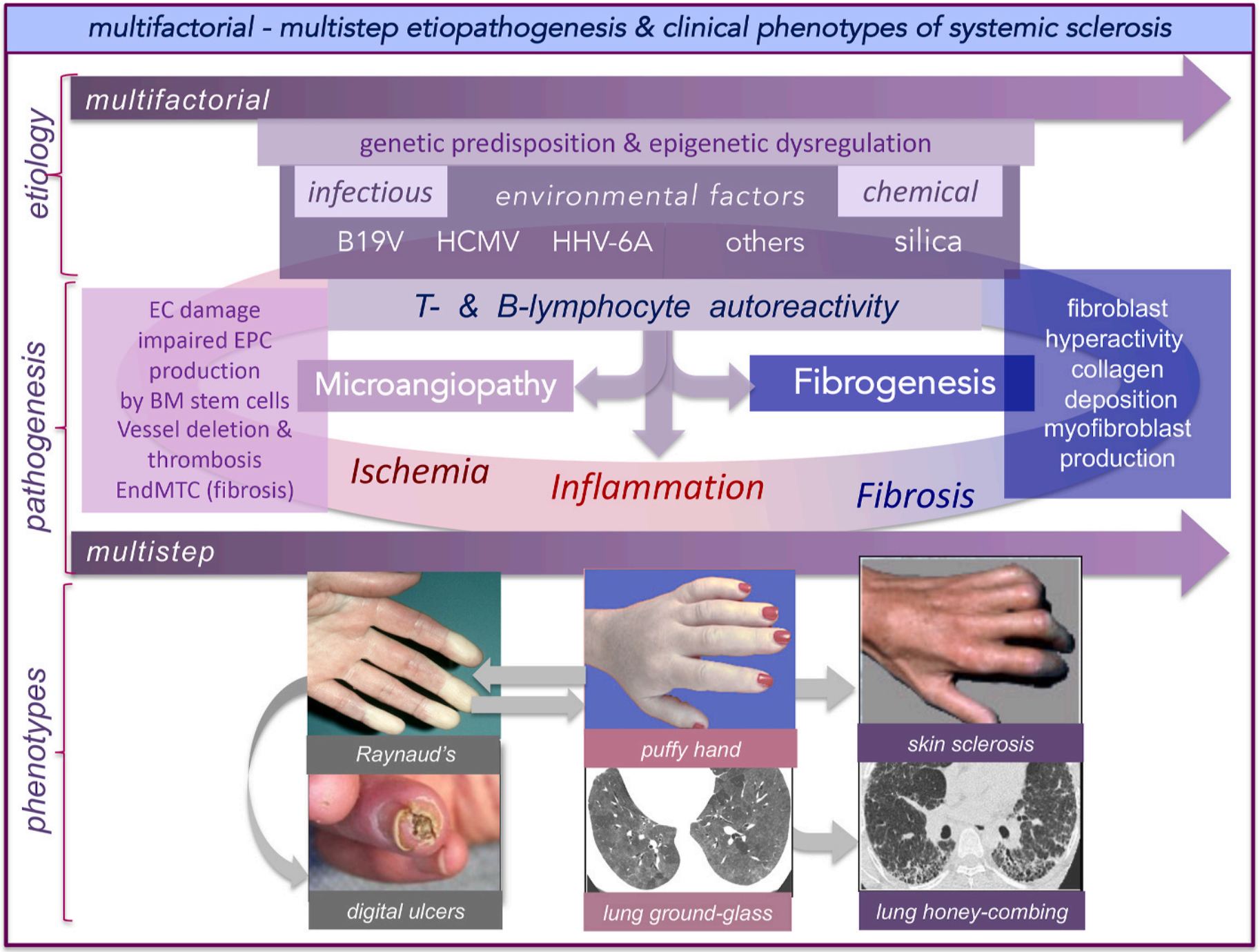


Fig. 2. Multifactorial and multistep etiopathogenesis of SSc with different clinical phenotypes and outcomes. The natural history of SSc commonly recognizes a very early, often subclinical, stage of disease characterized by diffuse micro vessel dysfunction (Raynaud's phenomenon is the early clinical hallmark that frequently precede the beginning of overt disease) and immune-system alterations, followed by progressive vascular manifestations (ischemic lesions of the skin and internal organ), inflammatory immune-mediated clinical features (puffy hands, lung alveolitis with ground-glass opacification), and ultimately more or less severe fibrotic damage (diffuse skin sclerosis with finger flexion contractures, lung fibrosis with honey-combing). This multistep process is often unpredictable in individual patients, it can be the consequence of a variable interaction between hosts' genetically driven autoimmune response to multiple combined/subsequent exogenous causative factors (see Fig. 1). The variable contribution of different etiological co-factors might explain the appearance of different clinical phenotypes and outcomes (skin ulcers, lung fibrosis, pulmonary hypertension, scleroderma renal crisis, etc.) among SSc patients and in the same patient during the course of the disease. *Abbreviations:* EC: endothelial cells; EPC: endothelial progenitor cells; BM: bone marrow; B19V: parvovirus B19; HCMV: human cytomegalovirus; HHV-6A: human herpesvirus 6; EndMT: endothelial-to-mesenchymal transition.

2021


multifactorial - multistep etiopathogenesis & clinical phenotypes of systemic sclerosis
etiology
multifactorial
genetic predisposition & epigenetic dysregulation
infectious
environmental factors
chemical
B19V
HCMV
HHV-6A
others
silica
pathogenesis
EC damage
impaired EPC
production
by BM stem cells
Vessel deletion &
thrombosis
EndMTC (fibrosis)
T- & B-lymphocyte autoreactivity
Microangiopathy
Fibrogenesis
fibroblast
hyperactivity
collagen
deposition
myofibroblast
production
Ischemia
Inflammation
Fibrosis
multistep
phenotypes
Raynaud's
puffy hand
skin sclerosis
digital ulcers
lung ground-glass
lung honey-combing

Multifactorial and multistep etiopathogenesis of systemic sclerosis

Possible role of SARS-CoV-2 infection in the worsening of natural clinical course of systemic sclerosis

2021

Lancet Rheumatol. 2021 Mar;3(3):e166-e168. doi: 10.1016/S2665-9913(21)00007-2. Epub 2021 Jan 12.

THE LANCET
Rheumatology

COVID-19 and systemic sclerosis: clinicopathological implications from Italian nationwide survey study

Ferri C et al. 2021
On behalf of COVID-19 & ASD Italian Study Group

Multifactorial and multistep etiopathogenesis of systemic sclerosis
Possible role of SARS-CoV-2 infection in the worsening of natural clinical course of systemic sclerosis

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Impact of COVID-19 and vaccination campaign on 1,755 systemic sclerosis patients during first three years of pandemic. Possible risks for individuals with impaired immunoreactivity to vaccine, ongoing immunomodulating treatments, and disease-related lung involvement during the next pandemic phase

Ferri C et al. 2023, on behalf of COVID-19 & ASD Italian Study Group